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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171

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EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/26/2002

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/558,149

Applicant(s)

NICOLAIDES ET AL.

Examiner

Ram Shukla

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 January 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13, 14, 18-20, 29, 52, 53 and 58-62 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13, 14, 18-20, 29, 52, 53 and 58-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*.

DETAILED ACTION

1. Amendments and response filed 1-07-02 is acknowledged.
2. Amendments to claims 13, 14, 19, 29, 52, 53, 58, and 59 have been entered.
3. New claims 60-62 have been entered.
4. Claims 13, 14, 18-20, 29, 52, 53, and 58-62 are pending.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 13, 14, 18-20, 29, 52, 53, and 58-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 7-5-01.

It is noted that the newly presented claim 62 is to a method of making a hypermutable, non-human, mammalian, fertilized egg, however, the claimed method is enabling since the egg so produced would be used to make a transgenic mammal and as discussed in the previous office action, making of a transgenic mammal as encompassed by the instantly claimed invention was not enabled.

Response to Arguments

Applicant's arguments filed 1-7-02 have been fully considered but they are not persuasive. In response to the enablement rejection applicants have indicated to page 9, lines 22-31 through page 10, lines 1-4, and lines 7-24 of the specification as support for the enabling disclosure. As was stated in the previous

office action of 7-5-01, the disclosure of the cited sections of the specification is a collection of general and cursory statements. It is noted that the applicants have not provided any factual evidence to support their arguments and applicants' statements and arguments cannot be considered evidence to support the enablement of the recited invention. It is emphasized that several arts were used in the previous office action to demonstrate the unpredictability of the art of making transgenic animal at the time of the filing of the instant application. Applicants have argued that the level of skill of one of ordinary skill in the art is high and armed with the disclosure and knowledge of the prior art, the skilled artisan would be able to make and use the claimed transgenic animals. It is reiterated that except for statements, applicants have not provided any factual evidence to support their arguments. In response to citing of *In re Buchner*, applicants' attention is drawn to other case laws regarding the issue of what need be disclosed. For example, Court have stated, "It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)).

Applicants have argued that the articles published in 1990 and 1993 hardly represent the state of the art at the time of the filing of the instant application. The examiner used articles published in 1990, 1993, 1997, and 2000, with an intention of demonstrating that the art of making transgenic animals has remained

Art Unit: 1632

unpredictable in the past ten years due to the same reasons. While the Examiner does not dispute the contribution of transgenics, it does not mean that the art of transgenics is not unpredictable any more and this is clearly discussed by Cameron. Applicants have again made statement that concerns of the examiner regarding promoters was within the purview of skilled artisan, however they have not provided any factual evidence. Applicants attention are drawn to MPEP 2164.03 which states:

"Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated: [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.] The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity)."

Applicants have not provided any factual evidence to support their arguments that the art of making transgenic animals was not unpredictable and that the disclosure in the specification was sufficient to provide enabling disclosure for making and using the claimed invention. Furthermore, several specific scientific issues were raised in the enablement rejection, however, applicants did not address these issues. For example, in the absence of any phenotype of the transgenic mouse encompassed by the claimed invention, an artisan would not have known how to use the claimed transgenic mouse, even if an artisan was able to make the transgenic mouse. Furthermore, the claimed invention would encompass transgenic mammals comprising full length mismatch repair gene PMS2 as well as a fragment of PMS2 or other gene recited in the claims. The specification discloses that this fragment of PMS2 acts like a dominant negative protein. It is not clear as to what would be the effect of expressing an additional PMS2 protein in a transgenic animal that would have its own endogenous PMS2, will the repair rate increase in any and all cells of the animal or a particular cell. Additionally, when the dominant negative form of PMS2 is expressed in the animals, what would be the effect on the metabolism of these animals or what would be the phenotype of these animals. In the absence of any guidance regarding the phenotype of the animals or characteristics of these animals, how would an artisan have used these animals. Furthermore, the specification fails to teach as to how the animals of the claimed invention would have been used. It is noted that it is well known in the art that there is unpredictability of phenotypic effects caused by variation in the genetic background used to generate or propagate gene targeted models and there are many examples in which animals containing same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse gene backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype. In other words, if the phenotype is to be used as a criterion in using the claimed mammals, in the absence of any predictable phenotype, an artisan would not know how to use the mammals. It is noted that the specification does not teach as to how these animals would be used when they were. On page 10, lines 7-11, the specification discloses that a transgenic

Art Unit: 1632

animal of the claimed invention can be used for generating new mutations in one or more genes of interest and such genes can be naturally possessed by the animal or introduced into it. However, the specification does not provide any guidance as to how the animals would be used for the intended utility. For example, if a DNA was to be introduced in an animal, how would it be administered to the animal or what doses would be used and how would the mutation be monitored. It is emphasized that at the time of the invention it was not routine in the art to use an animal in which a mismatch repair gene was mutated for identifying a new mutation in a gene and therefore, an artisan would have been dependent on the specification to use the animal and the specification fails to provide any guidance in this regard.

In summary, in view of the unpredictability of the art of making transgenic animals and lack of sufficient guidance and working examples in the specification, an artisan of skill would have required to carry out extensive experimentation to make a transgenic animal of the claimed invention and such experimentation would have been undue and the rejection is maintained for reasons of record set forth in the previous office action of 7-5-01 and as discussed above.

6. Claims 13, 14, 18-20, 29, 52, 53, and 58-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 7-5-01.

Response to Arguments

Applicant's arguments filed 1-7-02 have been fully considered but they are not persuasive. Applicants have argued that the specification clearly discloses transgenic animals including mammals which comprise a dominant negative allele of a mismatch repair gene (page 9, line 18 of the specification) and then the applicants indicate to page 8, lines 4-8 which discloses a dominant negative form of PMS2 etc. Applicants indicate to lines 1-12 of page 7 of the specification for written support for transgenic mammals. Applicants have also indicated to page 7, lines

Art Unit: 1632

13-27 of the specification. However, these arguments are not persuasive because the written description test is also to determine whether applicants have possession of the claimed invention at the time of the invention and there is no evidence in the specification or in the arguments presented by the applicants that the applicants had the possession of any species of the claimed genus of transgenic mammals at the time of the filing. Finally on page 11 of their response applicants quote from the federal register regarding establishing a prima facie case and state that a general allegation of unpredictability of the art is not a sufficient reason to support a rejection for lack of adequate description. In response, applicants' attention is drawn to MPEP which states:

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L. P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). In addition, the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention *Pfaff v. Wells Electronics, Inc* 48 USPQ2d 1641, 1646 (1998).

As noted in the previous office action, in analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure and since it is not realistic to expect that the complete structure of a cell could be described, this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In the instant case, the specification does not describe the structure of any transgenic mammal encompassed by the claimed invention. The specification does not disclose a hypermutable transgenic mammal either that comprises a protein that comprises the first 133 amino acids of PMS2 or any PMS2 gene. The specification does not provide any disclosure as to what would have been the identifying characteristics of the different species or a representative number of species of the claimed transgenic animals or the sequence of the mismatch repair genes encompassed by the claimed invention. As stated in the previous office action, since the art of making a transgenic mammal is unpredictable, an artisan

Art Unit: 1632

would not be able to predict what would be the identifying characteristics and structure of the invention claimed. One skilled in the art would not have been able to predict the truncation mutations required to change the wild type PMS2 gene of any and all mammal, if not, how would an artisan be able to describe the claimed genus.

Therefore, applicants' arguments that they were in possession of the claimed invention at the time of the filing of the application are not persuasive. It is reiterated that the applicants did not provide any factual evidence to support their arguments.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

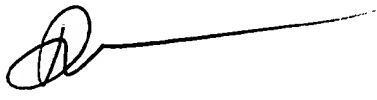
When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to <http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm>.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Art Unit: 1632

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.



DAVE T. NGUYEN
PRIMARY EXAMINER